REMARKS

I. Status of the Claims

New Claims 13-30 are pending in this application with Claims 1-12 being canceled without prejudice. Claims 1-12 have been rewritten as Claims 13-30. Support for new Claims 13-30 is found at least the specification, the paragraphs [0013]-[0028]. No new matter or new issue is introduced. Based on the remarks below, reconsideration and allowance are respectfully requested.

II. Claim Rejections under 37 C.F.R. § 1.75(c)

Claims 5-6 are objected to under 37 C.F.R. § 1.75(c) as being in improper form because a multiple dependent claim cannot depend from another multiple claims. Claims 5-6 have been cancelled, rendering the objection moot. New claims do not have a multiple dependent claim depending from another multiple claims.

III. Claim Rejections under 35 U.S.C. § 112, first paragraph

Claim 10 is rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner asserted that the claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Citing In re Wands, 858 F.2d, at 737, 8 USPQ2d at 1404, (Fed. Cir. 1988), the Examiner further asserted that

(1) Breadth of Claims: The scope of compounds is broad because hundreds of combinations of compounds can be created from the definitions, owing especially to broad scope of X, R_1, R_3, R_4 and m and n;

(2) Direction of Guidance: The amount of direction or guidance is minimal because no data on any specific compound is given and no dosage guidance is provided.

(3) State of Prior Art: There is no evidence of record that compounds structurally similar to these hydrazine compound are in use for the treatment or prevention of Alzheimer's disease.

(4) Working Examples: There is no any working example that indicates that beta secretase

inhibitors can treat AD and there is no biological data for any of the compounds.

(5) Nature of the Invention and Predictability: The invention is directed to method of treating or preventing Alzheimer in general and physiological activity us generally considered to be an unpredictable factors involved.

(6) The Relative Skill of Those in the Art: Alzheimer's Disease is an extraordinarily difficult disease to treat. Despite an enormous number of different approaches, the skill level in the art is so low relative to the difficulty of task that the only success has come from treatment by compounds which are Acetylcholinesterase inhibitors (Aricept®, Cognex®, Exelon® and Reminyl®), a property these compounds are not disclosed to have.

(7) The Quantity of Experimentation Necessary: No guidance from the success of others is available from this experimentation.

Claim 10 has been cancelled, which rendering the rejection moot. Cancelled Claim 10 has been rewritten as new Claims 24-25. Applicants respectfully traverse the rejections. Applicants respectfully submits that Claims have been rewritten to further define the subject matter of the invention drawn to beta –secretase inhibitors of formula (I). Moreover, as the specification of the application provides in paragraphs [0048]-[0051], beta-secretase inhibitors of the invention are characterized by IC50 values and identified by applying computerized screening, especially PHACIR screening, for the generation of a focused library out of a compound data base based on a comnined pharmacophere. Example 1 of the specification also provides Fluorescence BACE Assay and IC50 values for compounds of the invention. (see paragraphs [0061]-[0065] of the specification)

With regard to the Examioner's assertion on the state of prior art and the relative skill of those in the art, Applicants respsectfully point out that numerous studies support the proposal that inhibition of beta-secretase activity and reduction of amyloid beta in the brains provides a therapeutic method for treatment of Alzheimer disease and other beat-amyloid disorders. The specification of the application (see paragraph [0006] of the specification) discloses that (1) the aspartyl protease BACE (beta-secretase) is responsible for processing of amyloid precursir

protein (APP) at the beta-secretase cleavage site, (2) BACE 1 knockout mice fails to produce amyloid beta and present a normal phenotype, (3) when crossed with transgenic mice that overexpress APP, the progeny show reduced amounts of amyloid beta in brain extracts as compared with control animals.

Moreover, the method using beta-secretase inhibitors is a different therapeutic approach from the current therapuetics for Alzheimer's Disease based on cholinergic agents, specifically, inhibitors of acetycholinesterase (ACHE). The basis of the inhibitors of acetycholinesterase (ACHE) is the fact that AD causes substantial loss of cholinergic neurons, and ACHE inhibitors increase the levels of acetylcholine to keep the remaining cholinergic neurons firing. as explained in the paragraph [0008] of the specification. However, this type of therapy does not stop the progressive loss of cholinergic neurons, and eventually becomes ineffective.

On the contrary, beta-secretase inhibitors block the first cleavage of amyloid beta protein, thus blocking amyloid beta production and aggergation in the brain. Studies have reported that beta-secretase is the optimal theraputic target because (1) it catalyzes the initial, rate limiting step in Amyloid beta production, and (2) BACE-1 knockout mice do not show any apparent phenotype. (see the paragraph [0010]) In addition, as disclosed in the specification (see the paragraph [0010]), beta-secretase inhibitors are reported in other applications. ((i) PCT application WO 01/00665 C2 entitled "Catalytically active memapsin and methods of use thereof" describes the substrate specificity of the BACE enzyme, the first peptidomimetic inhibitors (OM99-1 and OM99-2) and the crystal structure of the inhibitors complexed with the enzyme, (ii) US20020115616 entitled "Novel inhibitors of Beta Amyloid Cleavage Enzymes" describes peptidomimetic compounds, (iii) WO 02/08810, WO 02/02520, WO 02/02518, WO 02/02512, WO 02/02506, WO 02/02505, WO 02/76440 and WO 02/47671) However, these compounds are relatively large and show poor ability to cross biological membranes and the claimed invention provides effective beta-secretase inhibitors which should further be able to cross biological membranes. Nonetheless, there is a great deal of knowledge in the art to guide those skilled in the art to make/use the claimed beta-secretase inhibitors.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph be withdrawn.

IV. Claim Rejections under 35 U.S.C. 112, second paragraph

Claims 1 and 7 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner asserted that Claim 1 uses the terms "preferably," "in particular" and "etc", which rendering claims indefinite and Claim 7 claims substance of library, which is not clear as to the meaning of substance of library.

Claims 1 and 7 have been cancelled, which rendering the rejection moot. New Claims do not have the language "preferably," "in particular" and "etc."

The Examiner rejected Claim 2 because of insufficient antecedent basis of the limitation "hydrogen for R4" in structure of the compound. Claim 2 has been cancelled, which rendering the rejection moot. New Claims do no have insufficient antecedent basis of the limitation "hydrogen for R4" in structure of the compound.

The Examiner rejected Claims 7-10 because the Claims are directed to the use of compounds, therefore, Claims are indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. The Examiner also rejected Claims 7-10 under 35 U.S.C. §101 because the claimed recitation of a use results in an improper definition of a process.

Claims 7-10 have been cancelled, which rendering the rejection moot. New Claims do not have the use of compounds.

Therefore, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph be withdrawn.

V. Claim Rejections under 35 U.S.C. 103

Claims 1-5 and 12 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Hall et al. (WO 99/37603) or Karrer et al. (U.S. Patent No. 6,306,798) or Rector et al. (J. Med. Chem., 1981). The Examiner asserted that (1) Hall et al. (page 25 and page 1) teach structurally similar

compounds as claimed invention, in particular A1 and A2 being phenyl or pyridine and various substitutents, (2) Karrer et al. (column 25 and 26) teach structurally similar compounds and composition, especially when R2 can be H, R3a and R3b are similar to substituents claimed in the invention, and (3) Rector et al. (Table I and II) teach structurally similar compounds and composition, especially when R or X can be alkyl or halo and equivalence of various substituents are clearly taught. The Examiner further asserted that it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to obtain compounds within the generic disclosure of the references, because they are structurally so similar to those claimed herein, with the reasonable expectation of achieving a successful composition, absent evidence to the contrary.

Claims 1-5 and Claim 12 have been cancelled, which rendering the rejection moot. Cancelled Claims 1-5 and Claim 12 have been rewritten to New Claims 13-17. Applicants respectfully traverse the rejection. Applicants would like to point out that the general formula in Hall et al. (WO 99/37603) or Karrer et al. (U.S. Patent No. 6,306,798) are different with respect to the substituent R1. Hall et al. discloses the formula of R1 being a CN-group and Karrer et al. discloses the formula of R1 being a CN-group, halo-C_1-C_6alkyl or –C(=S)-N(R_5)$_2$ (see column 1, lines 22-26), which are structurally different from the two bridging moieties as currently claimed in Claims 13-17. The Claims of the invention recite the bridging moieties as only an H-atom or a CH_3 moiety. Claims have been rewritten to overcome the rejection in view of Rector reference and Applicants respectfully submit that the Table 1 and II of Rector reference do not disclose the claimed invention. Therefore, the references cited by the Examiner do no teach and/or suggest each and every limitation of the claimed invention.

Furthermore, it has been known in the art for a long time that even a minor change in substitution patterns, i.e., for example, a change from methyl to ethyl or from CH_3 to CN, usually unexpectedly alters the physiochemical properties of an agent, especially in the pharmaceutical field. The Federal Circuit clearly states that "[F]or a chemical compound, a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter... where the prior art gives reason or motivation to make the claimed composition." (*Yamanouchi Pharmaceutical Co. v. Danbury Pharmacal Inc.*, 231 F.3d 1339 (Fed. Cir. 2000) The Federal

Circuit has also repeatedly stated that the requisite motivation for practicing an invention and the expectation of success must come from the prior art, not the applicants' specification. *In re Dow Chemical Co.* 837 F.2d 469, 473 (Fed. Cir. 1988).

The references cited by the Examiner do not present any reason or motivation to make the claimed composition. Moreover, the reasonable expectation of success with respect to the claimed invention is lacking in the references cited by the Examiner. Accordingly, Applicants respectfully submit that no prima facie case of obviousness has been established in the present application.

Applicants respectfully request that the rejection under 35 U.S.C. §103 be withdrawn.

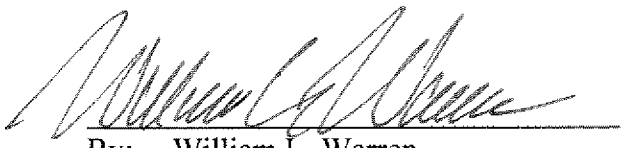
VI. Conclusion

In summary, the subject matter of the present invention is neither disclosed nor rendered obvious by any of the cited documents or by any combination of the documents if the skilled person would have combined them at all. In fact, one skilled in the art would not have any motivation to combine any of the cited references because none of the references teaches and/or suggests the subject matter as claimed in the present invention, and one or more of the cited references actually teaches away the present invention. Accordingly, for the reasons stated above, reconsideration and withdrawal of these rejections are respectfully requested.

It is believed that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the examiner believes, for any reason, that personal communication will expedite prosecution of this application, the examiner is encouraged to call the undersigned attorney at 404-853-8081.

The Commissioner is hereby authorized to charge any additional fees necessary to our Deposit Account No. 19-5029.

Respectfully submitted,



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